



November 5, 2015

USEPA
National Center for Environmental Assessment

Submitted electronically to: EPA_Sys-Review@icfi.com

Re: Recommendations for Topics and Speakers for EPA's December 16-17, 2015 "Advancing Systematic Review" Workshop

Dear Workshop Organizers:

The Center for Advancing Risk Assessment Science and Policy (ARASP),¹ which is managed by the American Chemistry Council (ACC)², welcomes the opportunity to provide input as EPA's National Center for Environmental Assessment (NCEA) plans its December 16-17, 2015 Systematic Review workshop. Incorporation of systematic review practices into the IRIS program is critical for improving the transparency, quality, and timeliness of IRIS assessments. Below we provide some recommendations and suggestions to strengthen the workshop.

1. The Workshop Should Focus Primarily on Implementing Approaches to Judge the Quality of Animal Toxicology Data

The majority of information available and relied upon in IRIS assessments is animal toxicology data. Therefore evaluating the quality (including risk of bias) of these data should be the highest priority for the IRIS program and this workshop. The Klimisch approach has been used by regulatory agencies in Europe, as well as OECD, since the mid 1990's indicating widespread support of this method by chemical evaluation and regulatory programs of the more than 30 countries that are OECD members, including the U.S. It is unclear why the IRIS program has not yet adopted this approach, or at least pieces of the approach, and instead the program continues to use unclear and inconsistent criteria for this

¹ ARASP is a coalition of twenty-two organizations focused on promoting the development and application of up-to-date, scientifically sound methods for conducting chemical assessments. More information on ARASP can be found: <http://arasp.americanchemistry.com/>

² The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing.



important data stream. If EPA believes that important Risk of Bias (RoB) elements need to be included, then this workshop should provide an opportunity for a clear and focused discussion about 1) the utility and applicability of the Klimisch approach and 2) what modifications may be needed to enable it to be used confidently within EPA chemical evaluation programs.

We provide the following recommendations for speakers and topics to help EPA move forward with transparent quality criteria to evaluate this evidence stream:

- Include experts from ECHA and the REACH program that have been using Klimisch for regulatory purposes. For example, ECHA staff implementing ECHA guidance on evaluating available information³ would be helpful participants. Industry experts who have been working to provide this information to ECHA as part of chemical specific dossiers submitted under REACH would also provide great value. In particular, we recommend Nicholas Ball from Dow Chemical in Europe.⁴
- Experts from the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) have expanded the Klimisch justification phrases using alphanumeric scores for each reliability category and ECETOC has employed these within its Joint Assessment of Commodity Chemicals program.⁵ ECETOC experts with experience using this expanded Klimisch scoring system, therefore, would also bring great value added to this workshop; we recommend Dr. Jim Bridges or Dr. Mark Pemberton.⁶
- Include experts from the OECD who worked on the OECD High Production Volume (HPV) Chemicals Programme where the Klimisch approach was used to ensure that there is sufficient good quality information on each of the elements that make up the Screening Information Data Set (SIDS).⁷
- Include experts from EPA who have evaluated the ToxRTool's ability to rate the reliability of toxicological data.⁸ In their publication, these EPA scientists concluded "ratings were most consistent for high-quality journal articles, but less consistent as study quality decreased." These authors went on to suggest the need for specific refinements and the workshop provides a perfect opportunity for further discussion with the EPA staff who have conducted this important evaluation.

³ See 2001 ECHA Guidance on information requirements and chemical safety assessment, Chapter R.4: Evaluation of available information. Available at: https://echa.europa.eu/documents/10162/13643/information_requirements_r4_en.pdf.

⁴ Nicholas Ball can be reached at: nball@dow.com.

⁵ See for example Appendix A Criteria For Reliability Categories available at: <http://members.ecetoc.org/Documents/Document/JACC%20051.pdf>

⁶ Dr. Bridges can be reached at j.bridges@surrey.ac.uk and Dr. Pemberton can be reached at markpemberton@systox.com.

⁷ See OECD HPV Evaluation Guide available at: <http://www.oecd.org/chemicalsafety/risk-assessment/36045203.pdf>.

⁸ See Segal D, Makris SL, Kraft AD, Bale AS, Fox J, Gilbert M, Bergfelt DR, Raffaele KC, Blain RB, Fedak KM, Selgrade MK, Crofton KM. Evaluation of the ToxRTool's ability to rate the reliability of toxicological data for human health hazard assessments. Regul Toxicol Pharmacol. 2015 Jun;72(1):94-101. doi: 10.1016/j.yrtph.2015.03.005. Epub 2015 Mar 14.

- Include EPA experts that worked to develop EPA's draft Development Materials for the IRIS review of Inorganic Arsenic. In April 2014, IRIS staff provided draft documents that included a RoB evaluation of animal data for inorganic arsenic. Public comments were provided to EPA on these draft documents; however, EPA has not yet responded to these comments. It would be useful to hear from this assessment team the lessons they have learned from the approach, what, if any, remaining concerns they have, and how they are currently considering implementing it in the future.
- Include experts that have been working to develop scoring tools for non-guideline animal toxicology studies. ARASP has been working with experts at Ramboll Environ who have given much thought to quantitative and qualitative evaluation tools for evaluating guideline and non-guideline studies. We recommend including Dr. Robinan Gentry⁹ in these discussions.

2. The Focus on the ACROBAT-NSRI Approach is Overemphasized

As most IRIS data are animal evidence, it is unclear why EPA is using the ACROBAT-NSRI tool as a starting point to evaluate methods. Even if the focus were just on epidemiologic data, a tool designed to evaluate non-randomized studies of intervention does not appear to be the best starting point. Although adoption of a tool designed to evaluate clinical epidemiology to environmental/occupational epidemiology is possible, it is likely to be of low value and utility. The document presumes an understanding of clinical terminology and a fairly advanced knowledge of methods and clinical research which is not necessary for IRIS-type datasets. We recommend speakers and topics that have worked on the following projects:

- Include experts knowledgeable in approaches for evaluating human data and environmental exposures. We recommend authors of the following approaches:
 - Money CD, Tomenson JA, Penman MG, Boogaard PJ, Lewis RJ. A systematic approach for evaluating and scoring human data. *Regul Toxicol Pharmacol*. 2013 Jul;66(2):241-7.¹⁰
 - Prueitt RL, Lynch HN, Zu K, Sax SN, Venditti FJ, Goodman JE. Weight-of-evidence evaluation of long-term ozone exposure and cardiovascular effects. *Crit Rev Toxicol*. 2014 Oct;44(9):791-822.¹¹
- Include experts who can speak broadly to the adoption of approaches and tools that may be best for the types of data available for environmental chemicals. We recommend Dr. Douglas Weed¹².

⁹ Dr. Gentry can be reached at rgentry@ramboll.com.

¹⁰ Dr. Money can be reached at chrismoneyuk@gmail.com.

¹¹ Dr. Prueitt can be reached at rprueitt@gradientcorp.com.

3. The Workshop Should Focus on Specific, Publicly Available Examples

Rather than talking in theory or generically, we believe this workshop would benefit from using case studies and specific examples. All this information should be made publicly available at least 30 days in advance of the workshop. Examples currently exist for systematic reviews or pieces of systematic reviews for environmental chemicals and much can be learned by examining these reviews as case studies. In addition to our suggestion to evaluate the IRIS inorganic arsenic documents, our understanding is that other groups are providing additional examples to EPA. We support a workshop that is focused around the examination of specific case studies.

Finally, EPA mentions using a model of “key characteristics of carcinogens” as an organizing principle for mechanistic data but neglected to provide any citations or documentation. To ensure full participation and robust dialogue, EPA should make all underlying information available to all workshop participants, with sufficient time for review, in advance of the workshop.

4. Evidence Integration Remains an Important Systematic Review Area for Discussion

EPA has not proposed any discussion on evidence integration. While this may likely be due to time constraints, the topic remains an important area in need of further discussion and deliberation among stakeholders. If scheduling allows, this topic should also be included.

- Include experts who have studied approaches for integrating evidence. We recommend authors of the following approaches:
 - Lavelle KS, Schnatter AR, Travis KZ, Swaen GMH, Pallapies D, Money C, Priem P, Vrijhof H. Framework for integrating human and animal data in chemical risk assessment. *Reg Tox and Pharm* 2012;62:302-312.¹³
 - Rhomberg LR, Bailey LA, Goodman JE. Hypothesis-based weight of evidence: A tool for evaluating and communicating uncertainties and inconsistencies in the large body of evidence in proposing a carcinogenic mode of action—naphthalene as an example. *Critical Reviews in Toxicology* 2010;40(8):671-696.¹⁴

Thank you in advance for your consideration of ARASP’s comments. We look forward to participating in this important workshop and hope the final agenda will reflect our recommendations. If you have any

¹² Dr. Weed can be reached at douglaslweed@aol.com.

¹³ Dr. Lavelle can be reached at: Karlene.s.lavelle@exxonmobil.com.

¹⁴ Dr. Rhomberg can be reached at: lrhomberg@gradientcorp.com.

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questions, or need clarification of our comments, please contact me at 202-249-6417 or nancy_beck@americanchemistry.com.

Sincerely,



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On behalf of ARASP

ARASP members:

Acrylonitrile Group
American Cleaning Institute
American Composite Manufacturers Association
American Forest and Paper Association
American Petroleum Institute
CropLife America
Halogenated Solvents Industry Alliance
Nickel Producers Environmental Research Association
Styrene Information and Research Center
Wood Preservative Science Council
ACC Chlorine Chemistry Division
ACC Ethylene Oxide Panel
ACC Formaldehyde Panel
ACC Hexavalent Chromium Panel
ACC High Phthalates Panel
ACC Hydrocarbon Solvents Panel
ACC Olefins Panel
ACC Oxo Process
ACC Propylene Oxide/Propylene Glycol Panel
ACC Health, Products, and Science Policy Committee
ACC Silicones Environmental, Health and Safety Center of North America
ACC Vinyl Chloride Health Committee

cc:

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IRIS General Comments Docket, EPA-HQ-ORD-2014-0211